UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
MEDICAL DEVICES ADVISORY COMMITTEE

OBSTETRICS AND GYNECOLOGY DEVICES PANEL

68TH MEETING

THURSDAY,
JUNE 3, 2004

The Panel met at 8:30 a.m. in the Whetstone Room of the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Kenneth L. Noller, Chair, presiding.

PRESENT:

KENNETH L. NOLLER, M.D., Panel Chair
SUSAN M. ASCHER, M.D., Temporary Voting Member
ANDREW I. BRILL, M.D., Temporary Voting Member
CAROL L. BROWN, M.D., Member
LAWRENCE A. CRUM, Ph.D., Temporary Voting Member
RALPH B. D'AGOSTINO, Ph.D., Temporary Voting Member
MICHAEL P. DIAMOND, M.D., Non-Voting Member
EVELYN R. HAYES, Ph.D., Member
PAUL J.A. HILLARD, M.D., Member
GRACE M. JANIK, M.D., Temporary Voting Member
KLEIA R. LUCKNER, J.D., M.S.N., Consumer Representative
HUGH MILLER, M.D., Member
ANNE C. ROBERTS, M.D., Temporary Voting Member
THADDEUS V. SAMULSKI, Ph.D., Temporary Voting Member
STEPHEN B. SOLOMON, M.D., Non-Voting Member
JONATHAN W. WEEKS, M.D., Member
BRANDFORD J. WOOD, M.D., Temporary Voting Member
JOYCE WHANG, Ph.D., Panel Executive Secretary
MICHAEL T. BROWN

FDA REPRESENTATIVES:

NANCY BROGDON, Director, Div. Of Reproductive, Abdominal and Radiological Devices
COLIN POLLARD, Chief, Obstetrics and Gynecology Devices Branch
JULIA A. CORRADO, M.D., Medical Officer
KATHRYN S. DAWS-KOPP
NOEL DEL MUNDO, M.D.
BRUCE A. HERMAN
LOREN A. ZAREMBA, Ph.D.

SPONSOR REPRESENTATIVES:

ROB NEWMAN, M.S., R.A.C.
BOBBIE S. GOSTOUT, M.D.
GINA K. HESLEY, M.D.
ELIZABETH A. STEWART, M.D.
CLARE M.C. TEMPANY, M.D.
KOBI VORTMAN, Ph.D.

I-N-D-E-X

P R O C E E D I N G S

(8:25:23 a.m.)

DR. NOLLER: Everyone take their seats, please. We have a very full day so I want to get started exactly on time. My name is Ken Noller, and I'd like to call the meeting to order. This is the Meeting of Obstetrics and Gynecology Devices Panel. I request that everyone in attendance please sign in. If you have not done so, please go out and sign in at the front desk now.

I also note for the record that the voting members present constitute a quorum as required by 21 CFR Part 14. I'm going to ask the panel members to introduce themselves. Let's start at this end, please.

MS. MOONEY: Mary Lou Mooney. I'm the Vice President of Clinical Regulatory and Quality for SenoRx, and I'm the Industry Rep to the panel.

MS. LUCKNER: Kleia Luckner, Hospital Administrator, Toledo, Ohio, and I am the Consumer Rep.

DR. D'AGOSTINO: Ralph D'Agostino from

Boston University, Biostatistician.

DR. BRILL: Andrew Bill. I am a Professor OB-GYN, University of Illinois.

DR. HILLARD: Paula Hillard, Professor of OB-GYN and Pediatrics, University of Cincinnati.

DR. DIAMOND: Michael Diamond, Professor OB-GYN, Wayne State University, Detroit Michigan.

DR. ROBERTS: Anne Roberts, Professor of Radiology, University of California - San Diego.

DR. NOLLER: I'm Ken Noller, Professor and Chair of Tufts University OB-GYN.

DR. WHANG: I'm Joyce Whang. And I'm an FDA Reviewer and the Executive Secretary for this panel.

DR. BAILEY: I'm Mike Bailey. I'm also a Reviewer in the OB-GYN Devices group, and I'm an Assistant Executive Secretary.

DR. BROWN: Hi. Carol Brown, I'm a Panel Member. I am an Assistant Professor at Cornell Weill Medical College, OB-GYN and a GYN Oncologist at Memorial Sloan-Kettering Cancer Center.

DR. CRUM: I'm Larry Crum from the

University of Washington. I'm Director of the Center for Industrial and Medical Ultrasound at the University of Washington.

DR. JANIK: Grace Janik, Clinical Professor at the Medical College of Wisconsin, Reproductive Endocrinologist.

DR. SAMULSKI: Thad Samulski, Duke University Medical Physics.

DR. HAYES: Evelyn Hayes, Professor of Nursing, University of Delaware.

DR. ASCHER: Susan Ascher, Radiologist, Georgetown University Hospital.

DR. WOOD: Bradford Wood, Interventional Radiologist, National Institutes of Health.

MS. BROGDON: I'm Nancy Brogdon. I'm not a member of the panel. I'm the Director of FDA's Division of Reproductive, Abdominal, and Radiological Devices.

DR. SOLOMON: Steve Solomon from Department of Radiology, Johns Hopkins.

DR. NOLLER: Thank you. For the press, the FDA press contact is Colin Pollard who is sitting

here in the front row. I don't expect that we'll have any super controversial outbursts today, but we would like everyone to please be courteous, turn off your cell phones, and if you have anything to say, wait until you're recognized and then come to the table. For the audience and the panel members I will recognize people before they speak. Our Executive Secretary has some things to read into the Minutes.

DR. WHANG: There will be OB-GYN Devices Panel on July 26th and 27th, so the remaining panel meeting date for this year is October 25th to 26th.

We are pleased to introduce a new voting member to this panel, Dr. Paula Hillard of the Department of Obstetrics and Gynecology and the Department of Pediatrics at the University of Cincinnati, College of Medicine.

Today we will have eight temporary voting members, Drs. Ascher, Brill, Crum, D'Agostino, Janik, Roberts, Samulski and Wood. And I will now read into the record the appointments to temporary voting status signed by Daniel Schultz, M.D., the Acting Director for the Center of Devices and Radiological Health.

"Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27th, 1990, and amended August 18th, 1999, I appoint the following individuals as voting members of the Obstetrics and Gynecology Devices Panel for this meeting on June 3rd, 2004; Susan M. Ascher, M.D., Andrew I. Brill, M.D., Lawrence A. Crum, Ph.D., Ralph B. D'Agostino, Ph.D., Grace M. Janik, M.D., Kenneth E. Najarean, M.D., Anne C. Roberts, M.D., Thaddeus V. Samulski, Ph.D., Bradford J. Wood, M.D.

For the record, these people are special government employees and are consultants to this panel. They have undergone the customary conflict of interest review, and they have reviewed the material to be considered at this meeting."

I will now read the conflict of interest statement for this meeting. "The following announcement addresses conflict of interest issues associated with this meeting, and is made a part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the Agency reviewed the submitted agenda, and all

financial interests reported by the committee participants. The Conflict of Interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. However, the Agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government. Therefore, full waivers have been granted for Dr. Susan Ascher and Anne Roberts, and limited waivers have been granted for Drs. Michael Diamond and Steven Solomon for their interest in firms that could potentially be affected by the panel's recommendations.

Dr. Ascher's waiver involves a contract to her employer funded for less than $100,000 per year with a competing firm. Dr. Roberts' waiver involves a stockholding in a competing firm in which the value is between $15,001 and $25,000. Dr. Diamond's limited waiver involves a contract to his institution for the sponsor study in which he had no involvement in data generation or analysis, and for which total

funding to the institution was less than $100,000. Dr. Solomon's limited waiver involves a contract to his institution for the sponsor study in which he had no involvement in data generation or analysis, and for which funding to the institution is unknown.

The waivers of Dr. Ascher and Dr. Roberts allow them to participate fully in today's deliberations. The limited waivers for Dr. Diamond and Dr. Solomon allow them to participate in the panel discussions, but exclude them from voting.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building. We would like to note for the record that the Agency took into consideration other matters regarding Drs. Diamond and Solomon. They reported current interests with firms at issue, but in matters that are not related to today's agenda. The Agency has determined, therefore, that these individuals may participate fully in the panel's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda

for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment on.

Transcripts for today's meeting are available from Neal R. Gross and Company of Washington, D.C., at (202) 234-4433, and videos are available from FDA Live at (301) 984-0001, or FDA Advisory Committee.com at (800) 627-8171.

Any presenters to the panel who have not already done so should provide FDA with a hard copy of your remarks, including overheads. Michelle Byrnes will collect these from you at the podium.

DR. NOLLER: Thank you. First, I'd like to introduce Colin Pollard, Chief of Obstetrics and Gynecology Devices Branch of the Food and Drug Administration.

DR. POLLARD: Thank you, Dr. Noller, and I just have a few brief comments to kick off our panel meeting today. I want to welcome all the panel member, and thank you very much for coming from near and far.

Today you'll be looking at a PMA for a high-intensity focused ultrasound system, really a new surgical modality that uses conventional MR Imaging for pre-op treatment planning and MR thermal mapping, really a new feature of MR technology for interactive treatment feedback. And treatment of uterine fibroids is the very first indication that's coming before this center in a PMA. The technology, obviously, looks capable of many other clinical applications and the center is currently working on a plan to optimize our regulatory review approach.

As you'll hear later in our presentation, we put together something of a designer review team for this PMA drawing from all parts of our center, especially from the technical side, and as we look around the table here I see several familiar faces, but lot of new faces. And really, we've put together

something of a designer panel, as well, and so we're very much looking for your input.

This PMA, the center granted expedited review to based on unique features and advantages. The FDA review is still ongoing, but we consider it quite appropriate at this stage to hear the panel input even as we continue to work our way through many review issues. And finally, that we feel this technology pushes the traditional envelope of clinical management, and if the panel gets to that point, we'll be definitely looking for input regarding training and labeling, and credentialing and that sort of thing.

So with those initial comments, Dr. Noller, I turn it back to you. Thank you.

DR. NOLLER: Thank you. Let me just ask that Drs. Miller and Weeks introduce themselves, please.

DR. MILLER: Hugh Miller from Arizona.

DR. NOLLER: And what do you do, Dr. Miller?

DR. MILLER: I'm a Maternal-Fetal Medicine Specialist.

MR. WEEKS: Jonathan Weeks from Louisville, Kentucky, Maternal-Fetal Medicine, Norton Health Care.

DR. NOLLER: Thank you both. First, let me ask before we open the public hearing, is there anyone present who will be speaking, request speaking at this session of the public hearing? All right. So if there's no one at this time, I will not read the conflict statement then. We'll move right ahead to the presentation by the sponsor.

I'd like to introduce Rob Newman from InSightec. The sponsor has been granted one hour and 15 minutes for their presentations. I ask the panel members to hold all questions until the end of the presentation.

MR. NEWMAN: Good morning, Chairman Noller, and thank you very much, ladies and gentlemen of the panel and the audience. I'm Rob Newman. I'm from InSightec in Dallas, Texas. My trip here has been paid for by my company. I am a member of the sponsor.

I'd like to introduce other members of our

team today. Dr. Elizabeth Stewart is an Associate Professor of Gynecology from Harvard Brigham & Women's Hospital. Dr. Clare Tempany is a Professor of Radiology at Brigham & Women's. They are Co-PIs of the study. Dr. Stewart is the Lead PI for the study.

Also, Kobi Vortman, the President of InSightec is here with us today. Karin Coyne, Senior Research Scientist from MEDTAP International, who has helped us with the quality of life work, and some of the biostatistics. Kathy McDermott from MedTrials, our CRO. We also have a guest here, Dr. Bobbie Gostout, who is Assistant Professor from the Mayo Clinic in Rochester, and Dr. Gina Hesley, an Instructor of Radiology, who are Co-PIs from the Mayo Clinical site.

This is an outline of our discussion today. I'll give a brief introduction. Dr. Stewart will talk about, in general, an overview of uterine fibroids and their application here. I'll give a brief overview of the device description. If you had a chance to review the video in the package, I think that will cover some of it, and there was quite a bit

of material in the panel package, so I won't go over that in any great detail.

Dr. Clare Tempany will talk about a review of MR anatomy, and what's commonly seen on MR that may be a little bit more than what some of you see in a regular clinical practice. She'll also discuss the treatment development process. Dr. Stewart will talk about clinical design trial results. I'll cover some elements of training, in addition to what was in the panel package, and then Dr. Stewart will summarize.

The indications for use for this device is its for use in pre or peri-menopausal women with symptomatic fibroids. The fibroids to be treated must be visible on non-contrast MRI and should enhance on contrast MR.

Outside the U.S., the system has received CE Mark in Europe in 2002. Its commercially available in Europe, Israel and Japan. In the U.S., the only applications are investigational. We have treated approximately 600 women worldwide for uterine fibroids. And I'd like to introduce Dr. Stewart, who will introduce the topic.

DR. STEWART: Mr. Chairman, panel members and guests, my travel expenses were paid by InSightec today. As Mr. Newman said, I serve as a Clinical Trial Investigator for the company, and am a Consultant for the company, but abide by the Harvard Medical School ethical guidelines that limit consulting when an investigator is involved in clinical research.

I want to start today by talking about the important problem of uterine fibroids. As everyone in this room probably knows, this is a very important clinical problem for women. That are very common tumors and the prevalence rates vary from anywhere from about 20 percent of women to being affected, to more recent estimates looking at high-risk populations by ultrasound where the prevalence of clinically detectible fibroids appears to be in the range of 75 percent.

Most of the discussion regarding uterine fibroids centers around cost and the costs are substantial for a healthcare system. It's estimated that the cost for hysterectomy alone in the U.S. along

per year is in excess of $2 billion. This is really the tip of the iceberg because it doesn't even start to take into account other surgical options, non-surgical options, medical options and various alternative treatments that women seek to try to control their symptoms.

I think it's important to note also that there is information regarding productivity in women with menorrhagia and so this is probably an under-estimate for the kind of women that we're seeing in our study who have clinically significant fibroids. The estimation from 2000 was that lost productivity due to menorrhagia or excessive menstrual flow is in the range of $1,600 per woman per year.

I think it's important to realize that fibroids are a common source of morbidity for women. They cause a lot of symptoms that tend to cluster in several different areas. Menorrhagia or excessive menstrual flow is an extremely important problem due to fibroids. And for women, this really limits their ability to carry out their work or their interactions with their families. There are many women that spend

up to two weeks every month with significant menstrual bleeding, and there are many women who have such significant menstrual bleeding that they cannot attend to any other activity for an hour or more without having to stop to deal with changes in sanitary protection.

Pain and discomfort are significant symptoms related to uterine fibroids. Many clinically significant fibroids are in the range of a three, four, five month pregnant uterus, and this gives women significant symptoms in terms of urinary frequency, urgency bladder discomfort, pelvic discomfort.

These symptoms have been shown to significantly impair health-related quality of life, and in several studies there have been demonstrations that women with uterine fibroids have significantly lower health-related quality of life than population norms. Uterine fibroids have also been linked to time away from work and other activities that are important to the economic system. And the Rand Corporation estimated that medical therapy may fail to control the symptoms in approximately two-thirds of women, so we

do need better therapies for uterine fibroids.

There are treatment options for uterine fibroids, but I think if you look at the range of options available for uterine fibroids in contrast to the woman who has a normal uterus and her options available for endometrial ablation, the contrast is clear. This panel has approved many devices for endometrial ablation, and many of those are restricted to women who have a structurally normal uterus.

Hysterectomy is a good solution for uterine fibroids. It is very effective in solving the symptoms, but it does have a significant morbidity associated with it, and a significant time away from work and family. For many women today to have the six week recovery for a major surgery is something that they cannot incorporate into their work and their family.

Myomectomy is an option for women who have a desire to retain their uterus but want resolution of their fibroid symptoms. Clearly, there are some women that are amenable to minimally invasive Myomectomies if the fibroid is in the right position at the serosal

or the mucosal surface. However, again this modality is a surgical modality, and can have significant recovery associated with it.

Uterine Artery Embolization has been an important option that has been added in the past decade for women with uterine fibroids. It has significantly decreased recovery time and fewer complications than hysterectomy. However, this modality is associated with pain and fever post-operatively, and there's increasing attention to the fact that there is an age-related impairment of ovarian function and this may be particularly an issue for certain groups of women.

Thermally ablative therapies have been tried previously for uterine fibroids. Many people have had experience with either myolysis or cryomyolsis, and there's a small experience with RF-ablation. These techniques have not really made it into the general gynecologist armamentarium, probably because of a lack of thermal monitoring.

With these prior therapies, there was no gauging of temperature, and so you couldn't tell had

you established a sufficient temperature to destroy the tissue. If not, you probably decreased your efficacy. Or if you exceeded the temperature goal, potentially you were injuring normal tissue and causing problems with adhesions or other follow-up.

Again, we do have drug therapies, but they tend to fall into two broad categories. Drugs such as oral contraceptives and progestins are widely used to control fibroid symptoms, but they tend to not be efficacious in the long-term.

On the other hand, GnRH agonists are very effective, but their side effects are significant, and their cost is significant, and so these drugs really haven't been great long-term choices for women with uterine fibroids.

We see that there's a spectrum of options available for uterine fibroids that for women with severe disease or who require a definitive solution, hysterectomy is still a choice. But many women are sitting down here with expected management and dealing with significant levels of symptomatology because they fear the surgical invasiveness of the other options,

or because they cannot, again, take the time and the recovery that's necessary to undergo a very invasive option.

We think MRI guided focused ultrasound surgery will be a very important option to offer women. It will give them the symptom relief that they require with significantly less invasiveness than many of the other options.

There are several unique things that are important to know about MRI guided focused ultrasound. It is a non-invasive, rather than a minimally invasive surgery. There is no surgical incision. There is no probe that goes into the fibroid. It is able to be accomplished as an out-patient procedure. Again, it serves the uterus and is uterine sparing.

The other important issue is that it is a fibroid-specific therapy. Unlike something like uterine artery embolization that targets the entire uterus, the fibroid is specifically targeted so that there is no impact on the myometrium or the endometrium.

Again, the real time feedback on

temperature gives you precise thermal ablation, and this is very important both for the optimization of safety and efficacy. Again, you can know that your temperature is getting to a therapeutic level and causing tissue destruction, and yet remaining in a safe range. And we have found that this procedure does not preclude or complicate future treatment options.

I will return the presentation to Mr. Newman, who will talk a little bit more about the device.

MR. NEWMAN: Thank you, Dr. Stewart. I'll just briefly review some of the key points of the device itself. As I said, much of this material is in the panel package, so I won't belabor the issues.

MR guided focused ultrasound is really a combination of two things, the idea of focused ultrasound as a source of thermal energy, and MR to plan and control the treatment in progress. There's two main components; one is the patient table and the electronics that's attached to the MR system. In the top of the patient table is the transducer, and

there's a water bath here. The patient lies on top of that. The energy is transmitted through the abdominal wall and focuses on a point inside the body.

Out next to the operator console of the MR is the control console for the focused ultrasound. Here's the regular MR console, and they sit side-by-side so that you can see your work on both systems during the treatment. Once the treatment begins, all of the control of the treatment and all the observation of the patient images is done from the ExAblate workstation. Next slide, please.

Just a brief history of focused ultrasound. Although this may be one of the first times that many of you have heard about it, focused ultrasound is a technology that's been around for a long time. There are publications as early as the 1930s. We didn't invent this. We're just kind of the latest people to carry on a long line of research in this. The Fry Brothers in the 40s and 50s did a lot of work on this looking at focused ultrasound in the brain and other places in the body.

Lele carried on work looking at several

tumors. There's also some carried on with some work using focused ultrasound for acoustic hemostasis and other applications. In 1993, Hynynen, Cline and others wrote the first paper on the combination of MR with focused ultrasound using MR for the thermal imaging. And then 1995 to present is ExAblate, the development of the device we're discussing today.

The transducer, a little of the physics of the transducer. The transducer lies here. The energy passes through the skin and intervening tissue to focus at a point. The energy is highly focused. It's kind of like taking a magnifying glass and focusing the sun's energy, so you can put your hand above the magnifying glass, below the magnifying glass, and it isn't until you get right at the point that the energy is highly concentrated.

The density in the far field, the energy is attenuated and absorbed along the beam path so while it's highly concentrated here, it falls off with distance in the far field.

The focused ultrasound energy propagates through tissue and skin. It's blocked by air, such as

in bowel or the rectum behind the focal point, and it's absorbed by bone, such as the pubic bone or the sacrum in the far field.

This is just brief picture showing the patient lies on top of it, so here's the transducer underneath. Here's the overall beam path for this entire volume, and in the blue is the focal path for a single sonication.

The one thing that's different about this as a source of thermal energy is we ablate one small piece at a time, as opposed to a cryoprobe where you create a large two, or three, or four centimeter lesion in one go, or RF ablation. We build up the treatment from a series of these individual sonications that are approximately 25 by 25 by 10 millimeters, so you're ablating about a half a cubic centimeter at a time. A single sonication takes about 20 seconds, and the target is to raise the tissue in-between 65 and 85 degrees Centigrade. If you raise tissue above 57 degrees Centigrade for one second, it's ablative.

There's a rapid fall-off. It's a highly

focused transducer, so there's a rapid fall-off with distance, so just a very few millimeters away from the focal spot you're back at normal body temperature. There's also a combining effect here because tissue's sensitivity to temperature is very time-dependent, so when you look at one pixel, it's the time temperature, it's the product of time and temperature that dictates whether you've had ablation or reversal heating of that point. So when do a treatment, the physician draws a region of treatment around the area to be treated, and then the system tiles it, if you will, with a series of these jellybeans, so that basically you draw a region of treatment and the system figures out how many jellybeans are in the jar. So how many will it take to completely cover this volume, so you can do a single layer, you can do multiple layers, and here's what it looks like in the horizontal plane, or looking down on it from above.

The treatment is controlled by MR thermometry. You're doing MR continously throughout the treatment, so it isn't like you do a single planning image or a stereotactic plan before. You're

using MR continuous throughout the energy delivery, so approximately every three seconds you're acquiring an MR image. The accuracy in vivo in fibroid tissue is about 3 degrees Centigrade. And what we're doing is we're measuring change in temperature with MR. We can't measure absolute temperature, but we measure change relative to body core temperature.

We take the information. We use this to tell us -- we can see the focal spot. We can tell where the energy is being delivered in three dimensions, and we can quantify the temperature to get this time/temperature information from each pixel.

At the end of each sonication, using this time/temperature information, we can calculate the volume of tissue that exceeded the dose, and we can use this information to plan the next sonication.

This is just a quick picture showing during a single sonication we're acquiring an image every three seconds here over a 15 second sonication in this case, so you can see at 1.7 seconds, you can see the spot start to show up on the MR image. At the end we take this information, calculate the volume of

tissue that was ablated, and we can draw one of these time versus temperature histograms here or maps, so we can where this little red cursor - it's hard to see in this slide - but there's a little cursor here, and you can see the time/temperature history out to 98 seconds.

If we would move that cursor somewhere here in the background away from the focal point, you'll just see some bouncing around, plus or minus a few degrees of normal body temperature.

We've done extensive thermal modeling in both 2D and 3D looking at a simulation of energy along the beam path to quantify the absorption of the energy, and to look at the tissue characteristics. We've done this to explore boundary conditions, to look at what type of dosimetry would be appropriate for maximum effectiveness, and to minimize thermal damage outside the treatment volume. And to really simulate things that we can't really do in vivo to look at kind of worst case scenarios of energy delivery and absorption that we wouldn't be able to do in vivo.

Pre-clinical evaluation was extensive where we looked at transducer designs, looking at transducer power, verification of ability to control the focal spot. There's a lot of work done in cavitation. Some of you may be familiar with focused ultrasound in other applications, such as lithotripsy. In that application, you're trying to generate cavitation. The whole point is to generate a very high energy shockwave to shatter a stone, such as a kidney stone. In our application, we only want thermal effects, and we want no cavitational effects, so there's a lot of design in the system and the use, limitations on the use to make sure that we limit our effects to thermal effects.

There was testing of the biocompatibility and a lot of animal testing in both -- for both our system and in the literature. There are several dozen publications over the last 15 years on the use of thermal imaging in MR.

Next I'd like to introduce Dr. Clare Tempany, who will give us an overview of MR anatomy for treatment planning.

DR. NOLLER: If I could interrupt for just a second. Our support personnel, could we have the temperature turned down a little bit, whoever is doing that.

DR. TEMPANY: Thank you. Good morning, Mr. Chairman, panel members, and guests. My name is Clare Tempany. I, too, am a Clinical Trial Investigator at the Brigham. My trip and accommodations have been paid for by the company. I work as a consultant like Dr. Stewart for the company, and work within the Harvard Medical School Guidelines for Conflict of Interest and Ethics in Research.

What I'd like to do for you today is two things. I'd like to introduce you to the MR imaging anatomy, display of anatomy and pathology that's used in this trial. It's used routinely in clinical imaging today, and then walk you through a typical clinical treatment.

Female pelvic MRI has become a very powerful diagnostic tool, and it's been available now to us in radiology for over 15 years. It exclusively

displays the female pelvic anatomy as you see in these what are called T2-weighted images for you on this slide. On the left you see a sagittal view, and on your right is a coronal view. And on the left, you can see the anatomy of the uterus and cervix displayed with the substructure of the zonal architecture of the uterus displayed with the layers delineated for you. And on the right you see the same thing with the ovary on either side.

Many of you are more familiar perhaps with pelvic ultrasound, and these are images of patients with fibroids where you can see an enlarged uterus here in the center, and then you see a slightly different appearing uterus in the right side here. The texture and tissue characterization of ultrasound is somewhat limited to either solid or cystic, where we can see the differences here with the cystic component on the right.

A little bit of MR anatomy and how we visualize these fibroids before we determine whether they're eligible for treatment or not, selected images here. Now we're going to walk through several planes

just to show you the display of the anatomy, and on the left you can see an axial view with the patient lying prone. The blue line represents the sagittal image on your right, and all of the relevant structures will be labeled, obviously, but you can see a very typical uterine leiomyoma sitting here in the center. It's classically a typical one that has a very low signal intensity or it's black, and it has a very sharp border. This is what we call a cookie-cutter sharp border which delineates and differentiates this from say adenomyosis, which will not have such a sharp border.

The coronal plane here you can now see nicely posteriorally as delineated up here on the blue line, but way in deep at the back of the pelvis here and the woman is standing in front of us, you can see the sacral nerves coming down here posteriorally, coming down along the lateral aspect of the pelvis to exit through the sacrosciatic notch. And as we come forward, you can see more anteriorally now. We're coming into the uterus. We see the large fibroid. We can see its relationship to the bladder. It's very

easy to understand some of the symptomatology this patient has experienced when you see images like this with a large uterine fibroid pressing on the bladder.

Now axial planes in a typical treatment position now with the patient is lying again prone, and you can see the uterine fibroid sitting here. We see the anterior skin there, and you can see the direction of the beam as you will see in a minute. And there's the fibroid. These are the anterior rectus muscles here anteriorally, and posteriorally we see the fat, the bowel, and the sacral nerves.

We've learned a lot about uterine fibroid or leiomyoma imaging over the years with MRI, and done many pathological correlation studies, and have determined that there are many types of fibroids, as you've known in the clinical world for many years. And these can be seen and characterized well in MRI. And to just summarize some of them here for you where you see about five different varieties described.

The top two are probably the typical ones that we would treat in this trial, or have treated in this trial, and these consist of the classic leiomyoma

which is a fiber muscular stroma. It's of low signal in every imaging sequence we have. In other words, it's black, it's easy to see.

A different type is what we call hypercellular, where it's also known as the white fibroid. It appears at high-signal intensity on T2-weighted images. Those are the ones we've treated.

The other group will represent ones that we wouldn't treat, which are non-enhancing leiomyomas basically, once that have already undergone spontaneous degeneration or necrosis in vivo, and obviously, of varying patterns also.

Just to show you some more examples of the range of the types of appearances of fibroids, here's a woman who's had very significant fibroid burden. Everything with an F on it is clearly a fibroid here. This is a coronal T2-weighted image, as if she's standing in front of us, her urinary bladder in white, and you see how this may appear like a five-month gravida uterus.

On the right side we see a different patient with multiple fibroids and an unusual

appearing one here posteriorally that's already undergone degeneration. This is a large cystic degenerated leiomyoma, and we know it's degenerated because we have post contrast images here in the middle that's after the injection of intravenous Gadolinium, and it shows no evidence of enhancement or it stays black with no perfusion; thus, indicating that it's necrotic. So let's just move into a treatment process now.

Much of that imaging will occur prior to the patient's being determined as eligible for the trial, and we have identified, selected the patient and identified the target treatment, and this is what now happens on the day. So starting the night before, the patient will receive written guidelines about the therapy and what to expect during the treatment. She will review that. She will have prepared the abdominal wall, removing abdominal hair from the umbilicus down to below the pubic bone. This is important because we want the skin to be as smooth as possible, and to not interfere with any coupling or cause decoupling of the ultrasound beam as it will

transmit through the skin.

She remains NPO from midnight because we use intravenous conscious sedation, and clearly don't want to have any problems with food. So we have the patient then come in the next morning. I meet with the patient. We review the treatment guidelines with her. We review what sort of sensations or experiences she may feel during the treatment. We develop the communication ritual to tell her when we're going to do a sonication, she tells me what she feels, and we sort of discuss all of that communication issue before we go in the room at all.

I also then consent her for administration of intravenous conscious sedation per our hospital guidelines. Once that is done, the IV line is sited, the Foley Catheter is placed. We use a Foley Catheter clearly to control the bladder during the procedure to make sure that the bladder stays empty. As you know, when the bladder fills, the uterus moves, and treating a moving target is clearly difficult, so we use the Foley Catheter to control that.

At the same time in parallel, the room

check is going on. There's a phantom checking of the system occurring, and after all of that is done, the patient then comes into the room, is positioned on the table in the coil, her vital signs monitoring devices are placed in position, obviously her pulse ox, blood pressure cuff, et cetera. The nurse will remain in the room with her at all times, and both she and the nurse will have a small little sonic button in their hands which will allow them to terminate an individual sonication should the patient experience an unusual severe pain. She has full control of the therapy itself at the time.

So here's just some pictures. You can see this is the MRI magnet, this is the table, patient sitting getting ready to go into position. She then turns over and lies prone, positioning the pelvis over the transducer. The transducer, as you've seen already, is in the table surrounded by degassed water so she lowers the skin down onto the water bath basically with a gel pad also in side it, and she makes direct contact with the skin into the water.

A little bit about our conscious sedation

and monitoring of the patient during the procedure. We use standard intravenous conscious sedation medications at our site. We use Versed and Fentanyl. These are administered to provide a combination of both analgesia and sedation. It's clearly important that the patient's anxiety and any claustrophobia that she may be experiencing in the magnet be aided by the administration of these medications. Patients, obviously, may experience positional pain lying on their stomach in the magnet for the duration of the procedure. And again, the analgesic effect is useful for that. And we obviously want to try to reduce any pain from sonication so we use the Fentanyl.

Typical doses that have been used in the procedures, and these are the total doses, range from as little as 25 mics of Fentanyl to 250 mics, to .25 to 5 of Versed. These are both intravenously. We also give patients an oral non-steroidal anti-inflammatory at the very beginning of the procedure. Usually, typically 75 milligrams of Voltaren has been used.

The medication then is given as required.

Before we start any treatment, we will give a very small incremental initial dose of Versed and Fentanyl, and then depending on how the patient is feeling, responding during the therapy, we will give further doses during the procedure, so that's why the ranges are quite wide here. Some patients require very little, some patients require a little bit more.

So let's just start now with treatment planning. The patient is positioned on the table, and you can see the transducer. And this is a good positioning on your left here, as opposed to the one on the right where the transducer is too high. And you can see this is a very large field of view image here. The uterus is really too low, and we would have to angle too steeply to treat that, so we clearly can readjust the transducer and the patient at this stage before we start going any further.

We will then take three planes of pelvic MRI images, as you've just seen, an axial, sagittal, and coronal to again define our target, to allow me to draw the contour to target volume superimposed on the fibroid at that point, and those images are coming up

in a minute. We'll show you how we do that.

Just to remind you that in the trials, we have protocol treatment guidelines. Single treatments initially were limited to 120 minutes. The maximal thermal dose per fibroid was limited to less than 100 CCs, and you could see treatment for all fibroids, if more than one was treated, was a total of 150 Ccs. We have a maximum of four fibroids that could be treated in any one setting.

The protocol treatment guidelines delineate a little bit further in detail here for you, and the schema on the right really explains it all nicely. The large black circle is a fibroid. The smaller one on the inside the region of treatment, the ROT, is the circle that I would draw as the sub-volume in the fibroid. We have to work with the guidelines, obviously, remaining within 15 millimeters of the outer serosal lining, and 15 millimeters of the endometrial lining. And so this clearly restricted somewhat the volume of the fibroid that we could actually treat during the initial safety and efficacy evaluations.

Here are some pictures of the same thing. You can see the treatment plan. Now the sonication grid has been overlaid and you can see these jellybeans, as Mr. Newman has already referred to, and you can see them overlaid here on the images. Before we do anything now, the next thing to do is to walk through each of these sonications and determine is the beam path going to be safe, and will it remain within the guidelines. So we work through this system here where we see the beam path on each and every one of these. And there are some images now, just to show you how that's done. You can see the passage of the beam going through in green here, and the focal point is delineated there on the sagittal view, the axial, and the coronal.

What can be in the way? Well, things that certainly can be in the way that we can identify relatively easily are things like scars that would be in the skin from prior surgeries, clearly things that are in the skin such as scar can cause defocusing of the ultrasound beam as it's passing through, cause local heating of the skin, and something that we try

to avoid at all costs. And so it's fairly simple to do this, we simply identify the scar ahead of time, and then using the roll and tilt mechanism of the transducer, we can angle around that area.

The same thing with bowel loops. Bowel loops are relatively easy to see here. You can see them on this T2-weighted image. They're the dark structures up at the top, and you can see again, we can angle either up and around the bowel loop, or if necessary, just simply not treat that area, clearly not go anywhere close to the bowel loop. The sonication can simply be deleted.

Same thing here if we're looking at the distal field. We can evaluate the location of the sciatic nerves, and we can determine whether or not the beam is going to pass through, and angle and roll, and tilt again to avoid it.

Okay. So now we're ready to go. The first thing we do is the geometric accuracy, and so this is when a low powered sonication will be delivered, and the very first set of images will come up as that's being delivered, and this is a cropped

down view here of the face map, and you can see that we're determining the accuracy; first of all, the visibility of the sonication. Can I see it at all? And you can hardly see it because it's covered by the red cross, but underneath that little red cross is a white dot, and that's the first sonication that's being delivered. And the initial assessment is good, now I see it. Is it in the right place? And so here you can that it's off by about 5 millimeters, so we will readjust all of the anatomical and adjust the geometric alignment so that the green overlies the red, and that they are absolutely concurrent.

The next step then is to move into a therapeutic sonication dose, so we increase the power up to typically 100, 140 watts, and we start the actual procedure with therapeutic doses being delivered. We compare this as it's going. We modify the treatment parameters as necessary. As you'll see in a minute, we're constantly looking at the feedback mechanisms of the thermal imaging, to determine if we've achieved a therapeutic dose or not.

Throughout the procedure I'm in constant

communication with the patient. This is very important because there's a one-on-one communication between myself, the patient, and the nurse in the room, but I will talk to her, tell her we're about to start a sonication at the beginning of one, and then at the end of that ask her if she's experienced any sensations, and if she has any concerns.

These are some examples now of the typical dose profile. On the left, you see a sagittal view or a long axis of a sonication, so you see the jellybean shape. This is a short axis view where you see it on end. And then these are three incidents of things that could happen, so if you look at the bottom left, we have a sonication that's achieving a thermal dose that's probably too hot. The temperature, you probably can't read that, I'm sure I can't either - it's 100 degrees is what that one has reached, so clearly, that's a little too hot. So what we do in that situation is to back down on the power before we go any further, so we wouldn't continue to treat without changing parameters once we've seen that.

Similarly, in the opposite direction, the

next one demonstrates a sonication that achieved a 50 degree temperature, and that's too cold, so the first step then would be to increase the power to bring it up to a therapeutic dose, which we like to see between 60 and 80 degrees.

Calcifications occur in fibroids, as you know, very frequently. They can be small punctate little pieces of calcium within a fibroid, or you can have a very more densely, heavily calcified one. The latter patient doesn't usually get into the trial because we can identify that in imaging, and a dense rim of calcification precludes treatment using this treatment modality. But small punctate calcifications are impossible to see ahead of time, and this is what may happen.

The ultrasound beam will be reflected off the sonication, will simply not achieve any therapeutic dose, so we simply move onto the next location, delete that sonication, so to speak, and don't treat that specific area. So an overview of the treatment cycle is seen here for you for an individual sonication. Before anything happens, the MR scanning

starts. Then the sonication is delivered, then a tissue cooling period occurs, and at all times the images are being acquired, and this total is about 2 minutes. So this is an extremely interactive treatment.

As you've seen already, the entire beam path is checked prior to delivery of sonication, irregularities of skin, bowel, and beam path are evaluated. We have multiple tools available to avoid critical structures, things that we would not want to have the beam pass through, and we use each and every image to modify the next sonication, so it's a very iterative process, so we're learning from the last sonication what to do for the next sonication. And we do this with the MR imaging that's continuously occurring during the procedure.

So there are some safety issues, obviously, where motion is a problem, if patients were to move during the procedure, as I've already said, heat treating a moving target is not good. So we obviously have prevented that now by the Foley Catheter placement with the bladder being controlled.

We also obviously coach the patient that she should not move her pelvis. She's lying prone, and if any of you have ever had an MRI scan, you know that we strap patients in on the table, that there's a coil around it, so it's fairly restrictive. There's not a lot of room to maneuver and to move around, so these are things obviously to our advantage.

We also use the restraint strap which is strapped around the outer pelvis to hold the patient on the table. The sedation somewhat helps also, but clearly she can still move if she really so desires. We monitor this with both sets of images. The real time images being acquired during the sonication are very easy to see motion, because it's like watching a movie. You're sort of seeing a cine loop, so to speak, so you can see changes if she was to move her skin or her spine.

We also place fiducials at the beginning of the imaging sequences, and these are the little red marks you see here. And those are monitored carefully, as well, to ensure that they don't change in position over the procedure.

The outcome assessment while the patient is still on the table, essentially as we're going we're developing this blue map in the center here which represents all of the therapeutic sonications that have been delivered, and have been therapeutic; in other words, reached the goal temperature delivery. And so the blue is the area that we will expect to see the necrosis. And at the end of the procedure, we confirm this by injecting Gadolinium and evaluating the necrotic tissue. And as you can see, nicely maps. The blue area here is now seen as the black area here, which is the non-enhancing or necrotic tissue.

Again, some other images from the end of a treatment. Typical treatments look like this. They can range from relatively small sub-volumes to slightly larger volume here, with the areas of necrosis seen in the area of treatment. And I thank you for your attention, and pass the podium back to Dr. Stewart, who will continue with the clinical trial design.

DR. STEWART: Thank you. In moving on to clinical trials in fibroids, that can be quite a

daunting task. As the Duke Evidence-Based Practice report has shown on, despite the fact of a wealth of clinical experience with uterine fibroids, this isn't a lot of good evidence on which to base therapy.

We were fortunate in going into our feasibility study having information from an in vitro model using a rodent model, and using ultrasound guided high-intensity focused ultrasound that showed treatment with this energy modality was feasible for uterine fibroids. And we wanted to get several important things out of our feasibility study.

First of all, we wanted to make sure that this was a safe treatment for women. We also wanted to confirm our targeting accuracy. As Clare has discussed, the feedback we get from the MR is important, and we are depending on the non-enhancing volume representing the tissue that we have successfully ablated, so we did want to get pathologic confirmation of this ablation. And this is actually something that hasn't been done with previous therapies, such as myolysis, cryomyolysis, or even uterine artery embolization. And we wanted to take

this information to help refine our pivotal trial design.

The study design was that it was an open trial for women who were scheduled for hysterectomy. They were to undergo MRI guided focused ultrasound three to thirty days in advance of their hysterectomies. In your panel packet, it appears that there are two distinct studies that our center and St. Mary's in London has described in one area, and then the other three sites are described in another area. However, because women were reluctant to go through treatment and hysterectomy, recruitment in the original cohort suffered, and so as time went on, these other sites began recruiting patients, as well. And then, in fact, the Israeli National Health Service made hysterectomy optional for that group of patients. They felt that it was unethical to require women to undergo this therapy and then not have the option of opting out of definitive therapy, so our trial design changed somewhat midstream, but we followed all of these patients, and reported them together.

We were able to confirm our pathological

information, and this is a diagram from our manuscript. This is the treated fibroid, and this is the pre-MR imaging that shows Gadolinium going throughout the fibroid indicating good perfusion. This is the post-treatment Gadolinium MRI where you see a large area of non-enhancement. And then this is the hysterectomy specimen. You can see on gross examination that there is a clear lesion that corresponds to the targeted area. And on microscopic exam, there appear to be coagulative necrosis corresponding to this area.

We were also able to confirm that there is a relationship between the targeted volume, the non-enhancing volume, and the pathologically correlated area of tissue destruction. In this particular fibroid from our St. Mary's site, you see the thermal dose volume in A, the B is a little bit bigger, the non-enhanced volume, and the pathologic area confirmed more closely to this non-perfused volume.

We did find that the non-perfused volume in general over-estimated the amount of tissue destruction, but we found that in all cases the area

of targeting was confined to the treated fibroid. There was one case where microscopic evidence of sonication was seen at the serosal border; however, in retrospect, it appears that that was incorrectly targeted. This was one of the cases where the bladder filled and the target moved, and is a reason why we adopted a Foley Catheter with our pivotal trial treatment.

So we were able to confirm pathologically that the tissue that we thought we destroyed was destroyed. We also were very pleased with our results in terms of patient treatment. All but one patient were able to be treated as an out-patient. There was a single hospitalization overnight for control of nausea. There was no post embolization syndrome. There, in fact, was very little pain in women undergoing this protocol. And most of the patients that we saw were not even taking over-the-counter medications at the time we saw them within 72-hours of their treatment.

The one safety issue that we did see in this initial protocol was there, there was a

significant incidence of infection seen post-hysterectomy. They did not occur between the focused ultrasound and the hysterectomy, but following the hysterectomy. And we stopped the trial at the time we saw the first three infections. We reviewed our procedures. At that time, we did change our protocol to institute prophylactic antibiotics. And once those were instituted, we didn't see further significant infections. And our pivotal protocol did not have prophylactic antibiotic use.

We also used the information in the trial to mitigate the adverse events we saw. We found early on that paying attention to the skin in various forms was important. Initially, patients were not shaving and there were small skin burns at the area where there may have been loss of coupling of the ultrasound to the skin. We also, again, found the importance of mapping the scars, and incorporating those into treatment planning. Because scar tissue is very similar to fibroid tissue, some of the energy would stop at that point and patients would be uncomfortable, and so we used a lot of the information

from this feasibility study to define the optimal treatment protocol to embark on our pivotal study.

The major issue when embarking on the pivotal study was the selection of a control group, and there are always issues with picking the perfect control group. And it's especially important, I think, to put this in the context of the times. At the time that the selection was going on, it was December, 2001. Although uterine artery embolization today might appear to be the best alternative, as a control group, this was not really possible at that time. There were no embolic agents that had received FDA approval at that time. And with extensive negotiations with the FDA and the investigators, we looked at the other alternatives. And we felt that looking at a surgical option would really give us important safety information. It was important to have a contemporaneously recruited control group, and not to depend in historical controls.

Again, abdominal myomectomy in many ways appears to be an important option. The issue for this group of patients was that many of them may not be

symptomatic. They would be pursuing treatment to attain fertility. They would also tend to be younger than the symptomatic patients that we were seeing. And with our group, we specifically wanted to recruit women with a threshold level of symptomatology. Therefore, we decided that although no control group was perfect, that abdominal hysterectomy would be the best alternative.

With our knowledge of difficulties in recruitment and our pivotal study, and also information we were gaining from the experience with uterine artery embolization trials, at this time many groups were trying to perform randomized trials between conventional surgical therapies and uterine artery embolization. And no one succeeded in having sufficient enrollment, so in that group of patients there were generally case series or parallel controls. And again, this is the study design that we settled on.

The hysterectomy group and the focused ultrasound group were enrolled in parallel. They met the same inclusion and exclusion criteria, and both

received the same six month follow-up. We also chose to separate the sites TAH and focused ultrasound so that you did not have investigator bias channeling good prognosis patients into focused ultrasound, and bad prognosis patients into hysterectomy, so the sites were all separated. And with our power calculations we found that a 3-2 ratio would give us the desired number of patient's in each arm.

The inclusion criteria included women who were not pursuing future pregnancy. We felt it was not ethical to treatment women who desired future fertility until we had information regarding the efficaciousness of this treatment. They were all pre-menopausal or peri-menopausal women. They did have both clinical exam and MRI consistent with fibroids. The fibroids needed to be visible on contrast MR, and feasible for treatment.

We also chose to have a minimum symptom severity score, so that they had to score over 40 points on a scale of 100 to be included in this protocol. The exclusion criteria were fairly obvious. Women who could not undergo MR were not included.

Women with excessive uterine sizes in excess of 24 weeks, or women that were too heavy to fit in to the MRI equipment were excluded. We also excluded anyone with an undiagnosed pelvic mass, or other worrisome pelvic pathology.

The primary hypothesis for our pivotal study was that we would see at least a 10 point improvement in the uterine fibroid symptom and quality of life symptom severity score. This is the only validated quality of life score specific for uterine fibroids. And we felt that in our treated group, we would have at least 50 percent of our patients achieving this goal.

We realized that the treatment modality would likely not be as effective as hysterectomy given the limitations, but we felt that this was an important landmark in demonstrating the efficacy.

We also evaluated several important secondary hypotheses. We wanted to look at the significant clinical complications in both arms to compare safety. We wanted to look at the trajectory of recovery, and also the costs involved.

For those of you not familiar with the uterine fibroid symptom and quality of life measure, this again is a disease-specific validated measure. It was developed specifically for uterine fibroids and it has two different parts. The symptom severity score, which you'll see in this presentation referred to as the SSS, has eight questions that relate to the fibroid specific symptoms, pain, bleeding and bulk.

There is also a component to the health-related quality of life which has six different sub-scales as is common with all quality of life questionnaires. And this questionnaire was developed from an ethnically diverse set of focus groups to really get input of fibroid patients, and what they felt their significant symptoms were.

Also during the validation process, this was correlated with the SF-36, which is really the standard measurement of quality of life, as well as a menorrhagia questionnaire indicating its comportance with symptoms of menstrual blood loss.

For those of you not familiar with the questionnaire, you'll see that the symptom severity

score addresses issues such as heavy bleeding during your menstrual period, passing blood clots. It also looks at bulk related symptoms, feelings of tightness and pressure, frequency of urination or nocturia or feeling fatigued. And patients are asked to rate their symptoms on a five point Likert scale from not at all to a very great deal.

This is data from the initial validation of this questionnaire that you'll see the two parts are divided here to the symptom severity score, and these are the sub-scales of the health related quality of life. One of the first things you'll notice is that there's an inverse relationship between them. For symptom severity score, the women in blue who are women with uterine fibroids, have a higher score, so higher scores mean higher symptoms. Whereas, with the health-related quality of life, the normal women tend to have higher scores and impaired related quality of life is reflected in a lower score.

It's also interesting to note the absolute levels of the symptom severity score. In this study, looking at women with symptomatic fibroids, the mean

score was 44; whereas, the mean score for normal women was 23 or about a 20 point difference between the two groups.

This clinical difference was the primary reason we selected our 10 point difference between treatment success and treatment failure; that if 20 points represents the difference between women with fibroids and normal, getting 50 percent relief of symptoms appears to be an appropriate clinical end-point.

There were also standard methodologic reasons to choose this. That 10 points is very similar to the standard deviation in the population. The standard error of the mean and gives a moderate effect size, as well.

We did not depend only on one outcome. We also looked at additional efficacy measures. We used the SF-36 which gives standard health-related quality of life. We looked at several measures of disability days, some assessment of an overall treatment effect, and also patient's treatment satisfaction.

This is a schematic drawing of the pivotal

study design that at the screening visit we perform the MR prior to the treatment, as well as the symptom screening. A hematocrit ruled out serious anemia, and during the treatment visit we again got information regarding symptomatology.

We took seriously that this was a new technology, and that there wasn't a lot of experience with follow-up, so we have everyone come back for a physical exam within a week so that we would not miss important issues that arose, so patients came back and did have a hematocrit and a physical exam at that time.

The one month and the three month follow-up were generally by phone, but then there was a full visit at six months with a physical exam and MR exam, and again complete testing.

The pivotal study design was originally designed to have outcomes at six months. However, later we have extended follow-up so that we're now seeing patients who are continuing on at 12 months, 24 months and 36 months. And again, getting information on quality of life, as well as MR exams at that time.

We wanted to try to capture significant clinical complications, and what we did at this time was we went to the literature. The paper by Dicker, et al, arose out of the collaborative study of sterilization. And they felt it was important at that time to try to define characteristics that could be used to compare treatment.

We used their criteria, but tried to update it both for the change and length of stay that has occurred since the 1970s, and also some of the differences that we would potentially see with this new therapy included as additions or things like discharged going to a rehabilitation facility, discharged with either a catheter or a drain, or also various interventional treatments that may not qualify under their definition of surgical procedures.

While this would seem to favor picking up complications from hysterectomy, I think it's important to remember that if there had been inappropriate targeting and significant injury of adjacent structures, these complications would have been seen and picked up if the treatment had

significant side effects in that way.

So moving onto the results of the trial, as we talked about earlier for the pivotal trial, there were separate sites for hysterectomy and MRI guided focused ultrasound. There were three U.S. sites and several through Europe and Israel. There were also hysterectomy groups and about half of the enrollment for both arms came from the U.S., and half from out of the U.S.

There was fairly equal distribution of patients through the sites. There wasn't a primary site that contributed all of the patients. And we looked at the demographics between the patients undergoing focused ultrasound, and the patients undergoing hysterectomy. We knew that since this was not a randomized trial, there were likely to be some differences. We did find them similar in age, and fairly typical for women with fibroids. There was a statistically different finding in body mass index with the women undergoing hysterectomy being somewhat heavier. And both groups of women had significantly elevated symptom severity scores.

As you'll recall in the validation study, the women with fibroids typically had scores in the 40s, and both of our groups this mean score was over 60. And again, there was a difference between these two groups with women who had elected definitive therapy for hysterectomy having a somewhat higher score.

There were more black women in the hysterectomy group. Again, probably a relationship of site selection, but all women in both groups were pre-menopausal by and large.

There were some differences in co-morbidities. The women undergoing hysterectomy were more likely to have diabetes and hypertension, and the women undergoing focused ultrasound were more likely to have thyroid disease. As you'll see later on, we looked at these differences between the focused ultrasound group and the hysterectomy group to see if these differences affect the treatment outcome.

We did perform an intention to treat analysis, so that every patient who received focused ultrasound is included, and so our denominator in the

slide you'll see is 109 patients. There were three withdrawals from the study less than six months, and 11 patients were non-evaluable. We did, however, do calculations for both evaluable patients and intention to treat patients, and they were similar.

The characteristics of the fibroid patients were consistent with women who had symptomatic fibroids. The average uterine volume was approximately 600 Ccs, but there were clearly a number of women who had uteruses in the range of 1,000 cubic centimeters or more. The average total fibroid load, meaning calculating the volume of the fibroids without the myometrium was in the range of 300 to 400 cubic centimeters. And patients had an average of two to three fibroids, but as many as 12. And although one to four fibroids could be treated during this protocol, in a average most women got one treated.

We excluded from treatment fibroids that were amendable to either hysteroscopic or laparscopic myomectomy, so although these say submucosal and subserosal, they were probably more accurately classified as partially submucosal or partially

subserosal with a large intramural component. And we also looked at differences in location when we assessed treatment outcome.

So when looking at the treatment parameters again with the intention to treat patients, the baseline fibroid volume was about 300 Ccs. The non-perfused volume at the end of treatment was in the range of 68 cubic centimeters, so we had approximately 24 percent of the fibroid that had been treated during this protocol. That at six months, there had been a decrease in size from about 330 to 295. This percentage of shrinkage is similar to the non-perfused volume. Again, it's not a large absolute number, but it is proportional to the amount targeted for treatment.

Looking at our primary efficacy and the symptom severity score, again we hypothesized that at least 50 percent of our patients would have a 10 point improvement. We were substantially in excess of that. Over 70 percent of our patients reached this targeted improvement, and this was statistically significant.

We also found that in fact the symptom

severity score at entry was in the range of 60. By three months there was already clear evidence of a treatment effect with a mean treatment level going down to 41, and then some continued improvement between three months and six months. And you can also see here, this is the criteria we set for entry, so many women at the three or the six month time point would not have had symptoms sufficient to qualify for enrollment if they had come at that point in time to seek treatment.

This is the distribution of changes in symptom severity score, so again this line indicates the threshold for success, or 10 points or more. These are the patients who had no improvement, or one to ten points of improvement, so everyone from here over is a treatment success.

The mean patient improvement, however, was about two and a half times what we had predicted and the mean treatment improvement was approximately 24 points. There were, however, some patients who improved as much as 60 points in symptom severity.

When we turn to look at the health-related

quality of life subscales, these parallel the changes that we saw in symptom severity score. Because of the inverse relationship these lines go up rather than down, so again you see a significant change or marked change between baseline and three months, and then some improvement from three to six months.

We use the SF-36 to be able to compare more accurately the patients between the focused ultrasound and the hysterectomy arm. What we see again in the focused ultrasound group is the same pattern of improvement that already at one month you're seeing improvement in some scales, continued improvement at three months, and stabilization from three to six months. In contrast, the women who underwent hysterectomy had marked impairment in some of their functioning at one month, and it took them three months to six months to get back to where they were and, in fact, to note improvement following the treatment.

The significant difference is in terms of disability between the two groups. I think it's important to note not only the differences between the

groups, but the absolute level for the focused ultrasound patients. When looking at the days -- this is follow-up at one month following treatment. There were only 1.4 days of missed work on average for the women in the focused ultrasound group. Whereas, women undergoing hysterectomy clearly has much more short-term disability with 18 days. And parallel the days that women with focused ultrasound were kept from their normal activities averaged about three days. And they again spent only about a day and a half in bed, so these numbers demonstrate the significant improvement and short-term recovery seen with this treatment.

We also looked at resource utilization through six months. Because of our different sites in different countries we didn't bring this down to dollars, but looked at encounters with the healthcare system. This takes into account not only all of the scheduled study visits for the MRI guided focused ultrasound patients, but for those patients that elected additional therapy, or went on to additional procedures. All of those resource utilizations are

captured.

We found that there was a significantly different length of stay. Only 1 percent of our focused ultrasound patients stayed more than five hours post treatment. They also had substantially fewer provider encounters, fewer additional procedures, and fewer diagnostic tests.

We looked at a logistic regression model to see if our baseline differences affected outcomes, so in the model we included not only the things that differed between our groups, such as race and BMI, but also looked at other variables of interest, such as age, country of treatment, fibroid location, percent non-perfused volume. And the only predictor of success was baseline symptom severity score. In other words, the most highly symptomatic patients were the patients that improved the most.

We also looked at patient satisfaction and asked patients were they satisfied with their treatment, was it effective in eliminating their symptoms, and would you recommend this to a friend? And again, over 70 percent of women answered

affirmatively to these three questions.

We did continue to follow patients beyond the pivotal study, and attempted to bring patients in for follow-up between six and twelve months. Again, we start with our intent to treat population of 109. We found that 91 patients continued on, 9 patients declined to be included in the follow-up. They had enrolled for a six month trial, and elected not to come back, and 9 were withdrawn, which left us with 82 evaluable patients at 12 months.

We found in following this group that 23 patients had gone on to alternative therapies, and four patients had elected and were offered additional focused ultrasound treatments. Both of these groups of patients are then included as treatment failures in our 12-month analysis.

So the original study was, indeed, designed for six month follow-up and we did contact as many patients as we could to come back. Because of the date that we started to do this, there was some lag, so although it's reported as 12-month follow-up, the actual mean follow-up was approximately 14 months.

The success rates do not look as promising at this point. If we look at our intent to treat group, there's only approximately a 38 percent success rate. And again, the patients who declined to come back for us to follow-up or chose alternative treatments are included here. And if you look at our evaluable patients, it is slightly higher at 51.

I think what's notable is that there were a substantial number of women who were still improved with the mean treatment being targeted at approximately 20 percent of their fibroid load. The other thing that is interesting about the results at 12 months is that we still could see significant decrements in the treatment parameters as measured by the symptom severity score, so that at baseline again, we're coming in at about 61 points, and going down to points in the mid to high 30s at six months and twelve months.

Part of the issue with the twelve month data may be that fibroid symptoms returned. This is clearly a common problem in the literature, and is well described for myomectomy. Again, it appears to

be an issue that may be applicable to uterine artery embolization, as well. But again, many of the studies with uterine artery embolization also have relatively short-term follow-up. And I think that our original treatment parameters were aimed at the maximization of safety and, therefore, may not have optimally targeted the amount of fibroids to get sustained treatment.

However, there were still significant patient satisfaction with treatment success at 12 months. Again you see in blue the six month data, and the twelve month data in yellow, so the patients were still very happy with the treatment option that they had pursued.

Turning our attention to safety, I think it's important, first of all, to note what we did not see; that many devices that are approved have significant complications. In many case series, there have been patient deaths or urgent unintended procedures. There were none of those in this treatment. There were no bowel injuries. There were no hospitalizations for pain control or post embolization syndrome. So compared to some concerns

that we had at the beginning, we were very happy that there were not severe safety issues that we encountered.

Looking at a strict definition of adverse events, we found that 19 percent of patients in the focused ultrasound group had no adverse events compared with 1 percent in the total abdominal hysterectomy. We chose for this protocol because of its novel technology to strictly define adverse events more similar to what you would see in a drug study than a typical device study. We knew that this was a device that didn't have clear predicates, and we wanted to make sure that we were not missing adverse events.

However, we found that when we looked at device or procedure-related serious adverse events, we still did very well with only 2 percent of MRI guided focused ultrasound patients having serious adverse events compared to 13 percent in our contemporaneously enrolled group.

We found that the body systems in which adverse events were found to be similar in most cases.

On average, women undergoing focused ultrasound had about two adverse events versus four for the total abdominal hysterectomy.

We also wanted to define what we thought prospectively would be device or treatment-related adverse events. We that non-significant events might include fever or pain in the treatment area, swelling or firmness in the treatment area, or minor skin burns. However, we felt that either skin burns that caused ulceration or any kind of nerve damage should be termed significant anticipated events, and that we were especially looking for these events as treatment unfolded.

Again, as we saw in our feasibility study, there was a substantial decrease in the amount of pain patients had both during this procedure and post procedure, compared to some alternative therapies. Interoperatively, the patients reported on average mild discomfort and mild to moderate pain. And then at post procedure, their levels of both pain and discomfort were significantly closer to no pain at all than to mild.

There were patients who had some severe pain during the procedure. And as Dr. Tempany discussed, we do have the ability to redose pain medications during the procedure. Only one patient, however, related her pain as severe post procedure. And again, we found that narcotic use following the procedure was very rare, and that even over-the-counter medication use was rare in the days following treatment.

We wanted to look at adverse events again to see if our baseline differences and the co-morbid conditions or the demographics affected these outcomes. Clearly, there were some co-morbid conditions in the hysterectomy group that may have made them more likely to experience complications. We found, however, that in controlling for this, the odds ratios still showed that there was significantly increased risk of dermatologic, gastrointestinal CNS and pain adverse events in the group undergoing hysterectomy compared to the group undergoing focused ultrasound.

Again, we wanted to look at the

significant clinical complications to make sure that we captured significant events, and again use the literature to prospectively define this. We found that the patients undergoing hysterectomy were more likely to have a significant clinical complication with about 46 percent of the group in the hysterectomy group having an adverse event, as opposed to 12 percent in the focused ultrasound group.

One of the interesting comparisons is looking at fever and antibiotic use, given that the patients in the focused ultrasound group did not receive prophylactic antibiotics; whereas, the patients undergoing hysterectomy traditionally did. And still, the incidents of fever and antibiotic use started after the prophylactic antibiotics for presumed infection were lower. The transfusion rate was also low. There were no unintended surgical procedures, no discharges with appliances. There were several rehospitalizations, but none requiring interventional treatment, and no death or life-threatening events.

We also found that there were differences

in -- there were significant differences in clinical complications. And our most serious adverse events included device-related adverse events; that we found that there were several instances of leg pain, which again we had identified as an anticipated event. There were also some skin burns, although most were first and second degree burns that resolved easily.

Our most important device-related, and our only device-related SAE involved a patient who had a treatment where there was injury to the sacral nerves. I think this is the case that pointed out to us the importance of having patients talk to us about their pain and discomfort. And that this patient did not receive pain medication at her request, and was noted at post treatment time to have weakness and nerve conduction studies confirmed injury.

However, by 12 months she has resumed a high level of physical activity, and in fact has run a marathon since her treatment. She had significant symptom improvement, and continues to be a part of our study.

We also put in a number of steps to

mitigate the risk of nerve damage. As Dr. Tempany talked, there are several things that can be done in the treatment planning and the use of feedback from the patient. Since we instituted these measures, there's been no significant nerve injury, and the incidence of nerve injury has been minimal. So we also did a number of simulations that allowed us to look at this issue. And so again, we had one event since learning from this important case.

Looking at the serious adverse events, again we classified everyone that was hospitalized as having an adverse event, an SAE, even if it was felt not to be device or procedure-related; again, sacral nerve injury, nausea. And then there were four women that went on to additional therapy, which we felt was really progression of disease and not device-related.

There is one complication on commercial treatment that resulted in a patient death. A single patient in one of our outside the U.S. sites had a pulmonary embolism following commercial treatment. This was investigated by the local M&M committee, and it was felt that her death was not related to the

procedure. And in fact, in retrospect it turns out she had several important thrombotic risk factors that had not been identified.

We do have a continued access protocol, and have continued to treat patients. It's very similar to our pivotal study with mild changes in the treatment parameters that allow slightly increased treatment time and treatment volume. And we've been enrolling patients in this protocol since April of `03 with 89 patients treated to-date. The adverse events in this group have been significantly less than in our pivotal study, and indicate that our mitigation steps have been successful. And we don't have enough of these patients to six months to comment on efficacy, but the three month efficacy appears similar to the pivotal study.

So in summary, we only had one device-related SAE, and a low incidence of adverse events. We confirmed that this treatment can be safely performed as an out-patient, and have learned from our experience to design a safer study protocol.

We also found that we met our primary

efficacy point with a significant margin. We had a much lower symptom severity score than we had predicted, and all of the measures of improvement tend to move together to show patient improvement.

I'll turn the program over to Rob to talk about the training.

MR. NEWMAN: I'd just like to speak briefly to amplify on the information that's in the panel packet about the training program. We believe that this is truly a non-invasive surgical alternative. This is a scalpel of sorts, a non-invasive one, but it is a scalpel. The physician controls the delivery of therapy, and the system provides the ability for real-time interactive control of that looking at the results from the treatment itself.

The system works only a 1.5T MRI system. We believe that this is necessary. It's the current state-of-the-art for pelvic imaging for assessment of anatomy and pathology. And it also gives us the image quality that we need for accurate temperature measurements. These symptoms have a high level of

service, and are in wide use throughout the medical community.

This system will only be used under the direct supervision of trained physicians. This is not something that would be used by anybody else. We believe that the gynecology and radiologic expertise is required, and the nursing requirements for these kinds of treatments are similar to what is currently being used in hospitals for regular interventional radiological interventional control, so there's nothing unique about that part of the treatment.

The training for all installations will include the entire team, doctors, the MR technologists and nursing. It's divided into two phases. One is the system operation, the technology side of it. The other part will be the clinical issues, which will be covered by preceptorships at clinical sites involving topics of patient selection, treatment planning, anesthesia, adverse event management and those kinds of things.

First, treatments will be supervised. And on our system, every sonication on our system is

recorded and kept in a file, so we have a log of every treatment we've ever done. This allow us both to review prior treatments if you had an adverse event, or if you've had something interesting. It also builds us a continuously growing teaching file that we can use for future sites.

Just a brief overview, the kinds of things would be what you expect we would cover in the classroom part of it on system components, and the physiology, device, protocol development, and we would follow this up with training after the procedures have begun at a specific site.

InSightec has a continued commitment to studying MR guided focused ultrasound. We think that this is -- there's an ongoing process here, a lot we can learn. As we've described before, we have the continued access protocol is in progress. We've treated 89 of 250 patients, and we intend to complete that 250 patients and collect three-year follow-up data on them to look at -- to gather more data on safety and efficacy of the system. And will provide us a lot of information on improvements in treatment

planning, and ways to make it more effective. And we also have additional studies ongoing outside the United States, and will include the analysis of that in our development of future features.

DR. STEWART: So in summary, I think we've demonstrated to you that the device that we're presenting has a low risk of serious adverse events. We were very careful to try to capture all events that occurred, and to report as completely as we could to make sure that this novel technology did not have any unintended side effects that we were missing.

One of the important issues with this technology is that it is fibroid-specific. And I think that that has benefits beyond what we've demonstrated today. The risk of complications is significantly lower than hysterectomy. And I think if we had chosen other control groups, we would have probably been able to demonstrate significant differences with other treatment modalities.

We've had a very low incidence of device-related events. And because this technique employs conscious sedation rather than anesthesia, there is

also a decreased risk of anesthesia-related events.

We have seen a clinically significant improvement in these patients. Patients are very vocal about voicing their improvement with this treatment, and we have been able to capture that by a number of different modalities. We designed our study and well-exceeded both our primary and our secondary end-points. And to be able to gain this kind of improvement without surgical incision, without major disability I think is a major step forward. The fact that these procedures can be performed as out-patients is important, as is the fact that it preserves the uterus.

Many women, I think, with fibroids tend to live with their symptoms rather than go through some of the treatment options. Some women have significant disability that they put up with day in and day out because of their concerns regarding invasive therapies. And I think MRI guided focused ultrasound surgery gives us an important new choice, and an important choice to help reduce the symptoms of uterine fibroids for women. Thank you.

DR. NOLLER: Thank you. We very much appreciate the sponsor staying within their time limit.

Our next presentation will be by the FDA. By the clock we are using up here, it is now 10:13. We will take a break until 10:30 by this clock, for 17 minutes, and then the FDA will make their presentation.

(Whereupon, the proceedings in the above-entitled matter went off the record at 10:07:53 a.m. and went back on the record at 10:26:03 a.m.)

DR. NOLLER: Okay. We'll reconvene now, please. And again, I'll ask the panel to hold its questions until after the FDA presentation. At that time we will I think have about 30 minutes to formulate and ask some questions. I'd like to introduce Kathryn Daws-Kopp, who will lead us through the FDA presentation.

MS. DAWS-KOPP: Good morning, ladies and gentlemen, distinguished panel members and guests. I'm Kathy Daws-Kopp, the Lead Reviewer for FDA on this PMA. My presentation will give a brief overview --

DR. NOLLER: Excuse me. Turn to the sound up. We can't hear her.

MS. DAWS-KOPP: Okay. Good morning. I'm Kathy Daws-Kopp, the Lead Reviewer for FDA on this PMA. My presentation will give a brief overview of FDA's review process on this PMA to orient you for the remainder of the FDA presentations.

You may notice as we go through our presentation that you'll be hearing some of the same things that the company said. Our intention is to focus on the issues we felt were important in our review of the file.

I'll start off by describing the history of regulatory interactions with the company, and I'll describe components of the device from a regulatory perspective. I'll provide a list of the PMA review team, and briefly discuss what we did in reviewing the PMAs, and I'll follow that with a list of some major issues that are still ongoing with this review, some of which are part of the panel discussion questions. I'll close with an agenda of the remaining FDA topics and presenters.

This is a brief overview of the history of FDA review on this device. The sponsor first came to FDA with a feasibility study in 2000. That file was reviewed by another branch in FDA, the General Surgery Devices Branch, who consulted with us on the file.

In late 2001, our branch took over review and the sponsor came to us to discuss a pivotal study. The study was given conditional approval in March of 2002, followed by full approval in May. We worked with the company on the protocol, and the study includes as you've heard both U.S. and foreign sites.

In 2003, when they had completed enrollment of the pivotal trial, the sponsor requested permission to conduct a continued access study which allows the company to continue to enroll patients while they're working on preparation of a PMA, and while the PMA review is ongoing.

For a number of reasons, the proposed protocol for the continued access study differ somewhat from the pivotal study. The continued access study was given conditional approval in June of 2003, and full approval in August. We received the PMA

submission on January 27th, 2004, and I'd just like to note that that file received expedited review status.

The ExAblate system is made up of the following basic components; patient table, operator workstation, software, equipment cabinet. The patient table is a standard MR table that has been modified to house the ultrasound transducer and associated equipment, and was already described by the company.

It should be noted that the MR system is a commercially available GE device, the Signa 1.5T MRI system is not commercially approved for thermography at the site. Software in the ExAblate device uses MR information from the GE device for mapping and targeting, as well as these new thermography functions.

This is the indication for use the company has already presented, but we'd like to go over this again. ExAblate is intended for use in pre and peri-menopausal women with symptomatic uterine fibroids. Patients must have a uterine size of less than 24 weeks, and be family complete. The fibroid or fibroids to be treated must be visible on non-contrast

MR and should enhance on contrast MR imaging.

This is a list of the review team. As you can see, a number of people have been involved in the review of this PMA application in the areas of clinical, statistical, epidemiology, MRI, ultrasound software, bioresearch monitoring, patient labeling, human factors, and manufacture.

This slide lists the things that we look at during our review. For software and hardware we look at safety and effectiveness. Examples of safety issues for software and hardware include electric shock, EMI shielding, and unintended burns. Examples of effectiveness are adequate targeting and thermal dose delivery.

We specifically look at requirements in testing. We check to see that the device is designed to do what the sponsor or manufacturer says it will do. And we look to see that they do tests that check to see that it works the way it's supposed to.

For bioresearch monitoring, we look at study execution, including recordkeeping and informed consent administration, as examples. For

manufacturing, we look at compliance with design controls both included in inspection. Bioresearch monitoring inspects clinical sites, as well as any records related to the conduct of the trial at the sponsor's facility. Manufacturing connects an inspection at the manufacturing facilities.

Bioresearch monitoring inspection is common for clinical trials, but is not required. A pre-approval manufacturing inspection is required. Drs. Corrado and Del Mundo will address clinical and statistical reviews during their presentations.

This is a list of our current major ongoing issues. This is not a comprehensive list of all issues. We are still discussing the thermal accuracy of the system with the company. Dr. Loren Zaremba will discuss this further in his presentation. We're still discussing adverse events that occurred, and appropriate medications to employ in response to these events. This will be discussed further by Dr. Noel Del Mundo. We will also discuss how the treatment in control groups differed, which Dr. Corrado will be discussing in her talk.

A pre-approval inspection is required, as I mentioned. FDA is working to get this inspection completed in a timely manner. Review of the labeling for a device is an integral part of the scientific review; however, we do not complete our review of labeling until we have finished the rest of our review of the file. These last two items, inspection and labeling will not be discussed further by other presenters today.

The rest of FDA's presentation will proceed as follows. Dr. Corrado will provide a summary of the clinical study and results. Dr. Zaremba will discuss the MR thermal mapping review. Bruce Herman will discuss the ultrasound-related review concerns, and Dr. Del Mundo will close FDA's presentation with a safety analysis discussion that will cover what we have considered most significant adverse events. Thank you for your time and attention, and I will now turn the floor over to Dr. Corrado.

DR. CORRADO: Thanks a lot, Kathy. Good morning, everybody. I'm Julia Corrado, and I'm a

member of the review team.

You have all already heard about the clinical trials of ExAblate from Dr. Stewart and Dr. Tempany, and I am going to be covering some of the same material, but I'm going to try to give an FDA perspective on that material. And I will try very hard to avoid unnecessary redundancy.

I'm going to be starting with a brief description of the feasibility study. I will then describe in more detail the pivotal clinical study, and the aspects of that study as you see here. And finally, I will give a very, very brief synopsis of the continued access study.

I'd just like to say who the -- normally we don't spend much time talking about the feasibility study at panel meetings, but this one was especially important because it signaled to us a couple of aspects of this treatment that we really wanted to scrutinize closely when it came to the pivotal study.

This feasibility study was prospective. It was non-randomized. It was conducted at two centers, and I'll just digress for a second. Dr.

Stewart described five centers. There was an IDE pivotal study that was conducted under FDA approval, and that was conducted at a center in the U.S. and one in Britain. And I'm speaking just about that feasibility study in my next couple of slides.

It was a pre-hysterectomy study. The women who volunteered were scheduled for hysterectomy, but they agreed to undergo the ExAblate procedure approximately a month prior to hysterectomy. And we approved the study for 15 subjects and 13 subjects received treatment.

The objectives were already described by Dr. Stewart. There were, in general, two types of tissue effect that are noted from ExAblate. I won't speak about them further, but there is a thermal coagulative necrosis and then there is an ischemic necrosis. The difference is that the thermal coagulative necrosis is caused by direct heating, and the ischemic necrosis results from lack of blood flow to surrounding tissue following heating.

In the summary of the feasibility study, the pathologist from Brigham & Women's described the

tissue effect as follows; that the volume of necrosis was sometimes larger than the treated area. That's a very important point that I'm going to be emphasizing. The treatment effect consists of bland and highly uniform coagulative-type necrosis with relatively sharp outline, scattered interstitial hemorrhage, and variable amounts of acute inflammation consisting mostly of neutrophils.

The next point also should be noted, and that is that the only abnormality noted in the myometrium outside of the fibroid, this was beyond the fibroid capsule, was microscopic coagulative necrosis extending one to two millimeters beyond the fibroid. This is the only case where we saw this effect, that there was a treatment effective beyond the fibroid capsule. But nevertheless, we thought it was important, as I'll describe further.

The purpose of the next slide is to illustrate something I just hinted at, and that is that the volume of effected tissue is different from the thermal dose volume; that is, the volume that was actually targeted. And there are two volumes that we

can talk about from the feasibility study. One is the non-profuse volume immediately following treatment. This is on, I believe, T1-weighted images with Gadolinium enhanced MRI. But also from this population, most of these women underwent hysterectomy so we also have volumes from hysterectomy specimens. And what I'd like you to notice here is that there is a consistent -- the non-profuse volume and the volume from histology are consistently greater than the thermal dose volume, which led us to feel that we wanted to be cautious in how the pivotal clinical study was conducted because we did not want to get injuries resulting from tissue necrosis beyond the targeted area.

As always, as we would expect during any kind of a clinical study of an investigational device, problems were encountered during treatment. For example, several patients received what was described as sub-optimal treatment due to excessive fat layers within the beam path. And in one case, the portion of the fibroid that the clinician wanted to treat was too close to intestine, and that limited treatment in that

case. In three cases, patients did not receive treatment due to tissue aberration and scar in the beam path that caused the patient to experience pain.

FDA, of course, always looks closely at adverse events and clinical trials, and we saw the following. But before I go into these adverse events, let me just note that despite that enhanced volume effect that I have described, we did not see any evidence of thermal injury to tissue adjacent to the uterine serosa, and this is one of the types of adverse events that we always watch very closely in devices that treat uterine pathology, so we did not see any such adverse events.

What we did see was bleeding post ExAblate, two first degree skin burns, a couple of cases of nausea and vomiting, and some post-hysterectomy adverse events that we would not be able to argue were related to the treatment. They were probably related to the hysterectomy.

As Dr. Stewart mentioned, there is also feasibility data from outside of the United States. And interestingly, in this study although 56 patients

received the ExAblate treatment, only four of those patients elected to undergo hysterectomy, and that was as of 14-month follow-up. So there is relatively less hysterectomy data from this feasibility study population.

The next couple of slides I'm not going to spend much time on, but I would just like to say that they demonstrate a trend, at least, towards non-profuse volume being greater than the thermal dose volume, although it was not uniform as it was in the smaller feasibility study conducted at Brigham & Women's and at St. Mary's in London.

In the feasibility studies that were conducted in Israel, again this was not conducted under FDA IDE regulation. However, there was one adverse event that in hindsight we probably under-appreciated at the time, and that was a case of sciatica post treatment. This patient had symptoms as of three weeks following her treatment, which at that time were described as improving, and at that time she was referred to a neurologist. I'm going to at least allude to this adverse event later in my discussion.